Approval Package for: 063066 /S011, 010, 009, 008, 007, 006

Trade Name: MINOCYCLINE CAPSULES USP 50MG

Generic Name: Minocycline Capsules USP 50mg

Sponsor: Warner Chilcott, Inc.

Approval Date: May 12, 1997

APPLICATION 063066 /S011, 010, 009, 008, 007, 006

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	Included	Pending	Not	Not
		Completion	Prepared	Required
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Tenative Approval Letter				
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Final Printed Labeling	X		, - + ·	
Medical Review(s)				·
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)	***			
Statistical Review(s)				
Microbiology Review(s)				
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Bioequivalence Review(s)	X			
Administrative Document(s)				
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Application Number 003066 /S011, 010, 009, 008, 007, 006

APPROVAL LETTERS

Warner Chilcott, Inc.
Division of Warner-Lambert Company
Attention: Norma Enders, R.Ph.
Rockaway 80 Corporate Center
100 Enterprise Dr., Suite 280
Rockaway, NJ 07866

MAY 12 mm

Dear Madam:

This is in reference to your supplemental antibiotic drug application dated April 21, 1997, submitted pursuant to 21 CFR 314.70(c)(Special Supplement - Changes Being Effected) regarding your antibiotic application for Minocycline Hydrochloride Capsules USP, 50 mg.

The supplemental application provides for container labels (50 mg - 20s) reflecting the option to use the proprietary name Vectrin® for your unit-of-use special contract package size.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved antibiotic drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

erry Phillips

Director

Division of Labeling and Program Support Office of Generic Drugs

Center for Drug Evaluation and Research

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/78/97

FROM: John Grace

, Consumer Safety Officer

SUBJECT: Special Supplement - Changes Placed into Effect

TO:

Document Room

Please make the following entry in the MIS concerning the status of this Special Supplement - Changes Placed into Effect.

ANDA(s)

SUPPLEMENTS(s)

APPL

GRANTED

DENIED

63-066 SLQ11

This form is to accompany the action package/jacket.

Thank you, /

Signature of CSO and Date

cc:

ANDA DIVISION FILE Warner Chilcott, Inc.
Division of Warner-Lambert Company
Attention: Norma Enders, R.Ph.
Rockway 80 Corporate Center
100 Enterprise Dr., Suite 280
Rockaway, NJ 07866

APR 14 des

Dear Madam:

This is in reference to your supplemental antibiotic drug applications dated November 27, 1996, submitted pursuant to 21 CFR 314.70 regarding your antibiotic applications for Minocycline Hydrochloride Capsules, USP.

Reference is also made to your January 8, 1997 amendments.

The supplemental applications provide for container labels ([50 mg - 100s and 1000s] and [100 mg - 50s and 1000s]) and package insert labeling reflecting additional capsule colors and proprietary name in the following manner:

- DESCRIPTION Deletion of specific dye components to create a second capsule color for each strength.

 were deleted from both the 50 mg and 100 mg capsules strength.

 and were deleted from the 50 mg capsule strength. The second capsule colors are orange for the 50 mg and blue for the 100 mg strengths.
- 2. The second capsule color container labels and insert labeling for each strength as well as the 100 mg package of 20s (unit of use) for special contracts will bear the proprietary name "Vectring".
- 3. HOW SUPPLIED Revised product description, color, imprint, and NDC numbers reflecting the second capsule colors.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved antibiotic drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Jerry Phillips

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

AADA 63-066/S-010 cc:

63-067/S-010

Dup/Division File _ .

HFD-610/JPhillips

HFD-613/APayne/AVezza/JGrace (no cc:)

HFD-643/RAdams/JHarrison

HFD-600/RF

HFD-82

njg/4/02/97/X:\NEW\FIRMSNZ\WARNCHIL\LTRS&REV\63066S10.APL

Approval letter - Multiple Supplements

AADA 63-066/S-009 (50 mg) AADA 63-067/S-009 (100 mg)

ADD 2 4 1996

Dear Sir:

This is in reference to your supplemental antibiotic drug applications dated March 20, 1996, submitted pursuant to 21 CFR 314.70 (c) (Special Supplement - Changes Being Effected) regarding your antibiotic applications for Minocycline Hydrochloride Capsules USP.

The supplemental applications provide for revised package insert labeling reflecting changes in the CLINICAL PHARMACOLOGY, PRECAUTIONS, and ADVERSE REACTIONS sections.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved antibiotic drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

4/24/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA: 63-066//S-006, 007, 008 (50 mg) 63-067/S-006, 007, 008 (100 mg)

Warner Chilcott, Inc. Attention: Norma Enders 182 Tabor Road Morris Plains, NJ 07950

JUN 24 1939

Dear Madam:

This is in reference to your supplemental antibiotic drug applications received March 1, 1996, submitted pursuant to 21 CFR 314.70, regarding your abbreviated antibiotic applications for Minocycline Hydrochloride Capsules, USP.

The supplemental applications provide for:

1. S-006: Elimination of the excess of active drug substance in the formulation.

2. S-007: Addition of batch sizes to and the for minocycline hydrochloride and before the

3. S-008: Stability data for the revised formulation supporting the expiration date of 24 months

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for approved abbreviated antibiotic applications described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincefiely yours,

kr, 6/21/96

Frank O. Holcombe, Jr., Ph.D. Director Division of Chemistry II Office of Generic Drugs Center for Drug Evaluation and Research



Nomera Enders P. P.

Normana. Enders, i Senior Director, Regulatory Affairs

PPL

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Special Supplement-Changes Being Effected

APR 21 1997

NOA NO. 63066 MET. NO. SLOIT

NDA SUPPL FOR LAFFIJAG K

Re: AADA #63-066

Minocycline Hydrochloride Capsules USP, 50 mg

Submission of Final Printed Labeling for Bottles of 20 Capsules

Dear Mr. Sporn;

Reference is made to our approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 50 mg. Reference is also made to our labeling supplement S-010, which was approved on April 14, 1997 and permitted the addition of a proprietary name (Vectrin®) for use with a second capsule color of our product.

This "Special Supplement-Changes Being Effected" provides container labels reflecting the Vectrin name for use with one of our approved package sizes (bottles of 20 capsules). For reference, please note that the bottles of 20 capsules were originally approved as part of our initial AADA approval and were supported by completed stability studies. In pre-approval correspondence dated February 22, 1989, it was stated that the bottles of 20 capsules would be available for "Unit of Use" special contracts. We wish to have the option of using the unit of use bottles for our Vectrin product; however, since this package size would not normally be commercially available, in accordance with 21 CFR 201.57(k)(2), we have not modified our insert to include the 20s package size.

Twelve final printed copies of our container labels for bottles of 20 capsules are provided in Attachment A and are arranged as follows: six copies are provided in the archive copy and six copies are provided in the review copy of this submission.

We trust that the enclosed labeling is satisfactory.

RECEIVED 3

APR 2 2 1997

Sincerely,

GENERIC DRUGGna A. Enders, R.Ph.

Sr. Director, Regulatory Affairs

Rockaway 80 Corporate Center • 100 Enterprise Drive • Suite 280 • Rockaway, NJ 07866 • 201-442-3233 • Fax: 201-442-3280

7 100med 7



Norma A. Enders, R.Ph Senior Director, Regulatory Affairs

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

January 8, 1997

SUTTAL AMENDEMENT

SL-010/AL

Re: AADA #63-066

Minocycline Hydrochloride Capsules USP, 50 mg

Amendment to 11/27/96 Labeling Supplement Proposing the Addition of a Proprietary Name Submission of Final Printed Labeling

Dear Mr. Sporn;

Reference is made to our approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 50 mg, and to our supplemental application submitted on November 27, 1996, which provided labeling reflecting the addition of a proprietary name (Vectrin®) for our product.

Our pending labeling supplement had provided draft container labels and insert labeling for the Agency's review. However, we recognize that only final printed labeling will be approved by the Office of Generic Drugs. Since we wish to implement the Vectrin labeling by February 28, 1997, we are now amending the aforementioned supplement with final printed labeling.

Twelve final printed copies of our container labels for bottles of 100 capsules and 1000 capsules are provided in Attachments A and B, respectively. Twelve final printed package inserts are provided in Attachment C. The twelve copies of each labeling piece are arranged as follows: six copies are provided in the archive copy and six copies are provided in the review copy of this submission. Please note that this labeling is identical in text to the draft labeling that was previously submitted. We refer you to our November 27, 1996 submission for a complete discussion regarding the differences between the Vectrin labeling and our currently approved labeling.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sinc RECEIVED

Norma A. Enders, R.Ph.

Sr. Director, Regulatory Affairs

ory



Norma A. Enders, R.Ph. Senior Director, Regulatory Affairs

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

November 27, 1996

NDA NO.____ NOA SUPPLIFE

Re:

AADA #63-066

Minocycline Hydrochloride Capsules USP, 50 mg
Labeling Supplement: Addition of a Proprietary Name

Dear Mr. Sporn;

Reference is made to our approved antibiotic drug application for Minocycline Hydrochloride Capsules, USP, 50 mg. Reference is also made to the Office of Generic Drugs' Policy and Procedure Guide #20-90 (as amended on 6/7/95), entitled "Variations in Solid Oral Dosage Forms and Injectables that can be Included within a Single ANDA."

The above-referenced policy guide permits multiple colors of a single shape for a single strength of a solid oral dosage form to be included in the same abbreviated antibiotic drug application. It is our intention to add a second capsule color to this AADA. The second capsule color will be marketed with a proprietary name (Vectrin®) and our originally approved capsule color will continue to be marketed under the generic name. Please note that this new color was obtained via the deletion of specific dye components from our currently approved product. In accordance with 21 CFR 314.70(d)(4), this change does not require prior FDA approval and will be reported in the next annual report. This submission strategy was confirmed via telephone conversation between myself and Mr. P. Rickman of your staff on October 31, 1996.

The purpose of this supplemental application is to provide the Office of Generic Drugs with the opportunity to review and approve labeling that bears the Vectrin brand name. In an October 31, 1996 telephone conversation with Mr. John Grace, also of your staff, I was instructed that this supplement should be submitted for prior approval. While we believe that the regulations permit this change to be reported in the annual report (in accordance with 21 CFR 314.70(d)(2)), we wish to fully comply with Mr. Grace's recommendations. However, please note that we desire to implement this new labeling by February 28, 1997; therefore, we would appreciate any efforts that your staff can make in providing an expeditious review.

Four copies of each of our draft labels and package insert labeling are provided in Attachments A through C. Please note that the attached labeling is identical to our currently approved labeling with the following modifications:

- 1) Addition of the Vectrin brand name and revised NDC numbers that are unique for the Vectrin product.
- 2) Revision of our company name and address to reflect the sale of Warner Chilcott by the Warner-Lambert Company and the subsequent relocation of our offices. (These actions were previously communicated to the AADA file in correspondence dated March 28, 1996 and November 21, 1996.)
- In addition to the above items, the package insert bears revisions in the "Description" section (removal of dye components from the inactive ingredients listing) and in the "How Supplied" section (revised product description, color, imprint, etc.).

Finally, we would like to point out that the Vectrin trade name was in use many years ago by Parke-Davis, Division of Warner-Lambert Company, when they distributed minocycline hydrochloride capsules under a licensing agreement with Lederle Laboratories. Warner Chilcott, Inc. has obtained the exclusive rights to the use of the Vectrin trademark. Since the Vectrin name was previously used for this same product, we were hoping that any review conducted by FDA's naming committee, if needed at all, could be handled in an expedited manner.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sincerely,

Norma A. Enders, R.Ph.

Sr. Director, Regulatory Affairs

VARNER CHILCOTT

LABORATORIES Division of Warner-Lambert Company

Sean Brennan, Ph.D. Senior Director Regulatory Affairs

> Special Supplement -Changes Being Effected

Douglas Sporn Director, Office of Generic Drugs Food and Drug Administration (CDER)

MAR 20 1996

Document Control Room Metro Park North II 7500 Standish Place, Room 150 Rockville, MD 20855-2773

Re:

AADA #63-066

Minocycline Hydrochloride Capsules USP, 50 mg

Labeling Supplement

Dear Mr. Sporn:

This is in response to your letter dated February 5, 1996 in which you commented on the labeling for our abbreviated antibiotic drug applications for Minocycline Hydrochloride Capsules USP, 50 mg and 100 mg.

In your letter, you requested that we revise our package insert labeling for the subject product in accordance with the approved labeling of Minocin® (Lederle Laboratories Division, revised December 1993; approved August 8, 1995).

We have completed these revisions and are submitting twelve copies of our final printed insert labeling in Attachment A for your review.

We trust that the enclosed labeling is satisfactory. We are concurrently submitting a similar supplement to our 100 mg strength application (AADA #63-067). If you should require any additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Sean Brennan, Ph. D. Senior Director

norma Ender for

Regulatory Affairs

REF. NO. 56 6 BIOADARTARILITY. formula time NDA SUPPL FOR ARNER CHILCOTT Senior Director **LABORATORIES** Regulatory Affairs Division of Warner-Lambert Company AEF. NO. 5 CO NDA NO. Charles Ganley, MD MAR 0 1 1996 Acting Director, Office of Generic Drugs Food and Drug Administration (CDER) Document Control Room Metro Park North II 7500 Standish Place, Room 150 Rockville, MD 20855-2773 NDA NO. Re: AADA #63-066 Minocycline Hydrochloride Capsules USP, 50 mg Supplement: Removal of the Excess of Minocycline Hydrochloride USP, in the Formulation and Increase of the Maximum Allowable Batch Size

Dear Dr. Ganley;

Reference is made to our currently approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 50 mg, which is manufactured at our facility in Lititz, Pennsylvania. At this time we would like to supplement our approved application to provide for a reformulation of the product to remove the excess of active drug substance, Minocycline Hydrochloride, USP. We would also like to incorporate a ncrease in our maximum batch size for this product. Information to support these changes are provided in Attachments 1 through 7, as indicated. Our 100 mg capsule product is covered by a separate AADA (63-067), which is concurrently being supplemented for these changes.

Our currently approved formulation includes a excess of Minocycline Hydrochloride, USP. We desire to change our formulation for Minocycline Hydrochloride Capsules USP, for the 50 mg and 100 mg strength capsule products by removing this excess, and making an appropriate adjustment in the amount of to maintain the target capsule weight.

In accordance with this proposed formulation change, we have revised our composition page and our Master Formula to reflect the deletion of the excess of drug substance and our desired batch size of These revised AADA pages are contained in Attachments 1 and 2, respectively. Other changes are being proposed in the revised Master Formula. Many of these changes are editorial in nature; however, some enhancements have also been incorporated. For the convenience of the reviewer, we have summarized these changes immediately prior to the proposed master formula appearing in Attachment 2.

In support of this supplement, we have manufactured a batch of Minocycline Hydrochloride Capsules USP, 50 mg, without the excess of Minocycline Hydrochloride, USP. Our executed batch record (including complete packaging records) for lot 976N2L is included in Attachment 3. Warner Chilcott's Certificate of Analysis for this lot is provided in Attachment 4.

AADA 63-066
Dr. Charles Ganley
Minocycline Hydrochloride Capsules, USP

Provided in Attachment 5 is Warner Chilcott's Certificate of Analysis for a reference lot of Minocycline Hydrochloride Capsules USP, 50 mg (lot 13013L). This lot is a routine production batch which was manufactured in accordance with our approved AADA; therefore, it contains τ excess of Minocycline Hydrochloride, USP.

Reference is made to the telephone conversation between Dr. S. Dighe, formerly of the Division of Bioequivalence, and Mr. V. Kumar, Warner Chilcott's former Director of Research and Development, on December 11, 1992 (as cited in a letter dated January 28, 1993). During this conversation, it was agreed that Warner Chilcott would conduct a bioequivalence study to support the removal of the excess from our current formula. We are submitting the final report of this bioequivalence study in our concurrent supplement to our 100 mg strength application (AADA 63-067). This single-dose, two-way crossover study compares the relative bioavailability of Warner Chilcott Minocycline HCl Capsules USP, 100 mg with and without 2 overage of Minocycline Hydrochloride, USP taken under fasting conditions (protocol #0801-5011).

Based on the results of this study and comparable formulations, we are requesting waiver of the requirement for an *in vivo* bioequivalence study for our 50 mg strength product, as permitted under 21 CFR 320.22 (d)(2). In support of this request we are including comparative dissolution data for 50 mg and 100 mg strength Warner Chilcott Minocycline Hydrochloride Capsules, USP with and withou' excess of Minocycline Hydrochloride, USP, in Attachment 6.

Finally, we have included stability data for the reformulated product stored at 40°C/75% RH for 3 months and up to 24 months at 30°C packaged in our currently marketed package sizes (bottles of 50 and 1000 capsules) in Attachment 7. Based on the attached stability data, we are requesting an expiration dating period of 24 months for the reformulated product, which is the same as for our current formulation.

We trust that the enclosed information is satisfactory. In accordance with submission requirements, a field copy of this supplemental application is being concurrently submitted to our home district office in Newark, NJ. If you should require additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Sean Brennan, Ph. D.

Senior Director Regulatory Affairs

	NDA NO	_REF_NO.5C-004	NDA NO	REF NO. OCO
	NDA SUPPL FOR	Manufacturens Ken	NDA SUPPL FOR	Formulation Ranging
WARNER CHILCOTT LABORATORIES Division of Warner-Lambert Company	Ser	nn Brennan, Ph.D. ior Director julatory Affairs	NDA NO.	REF NO SC-008 Exparation Date
Charles Ganley, MD Acting Director, Office	•	DECEIVED	MAR	0 1 1996
Food and Drug Admir Document Control Ro Metro Park North II	•	MAR 0 4 1996	PECEIVE	מ
7500 Standish Place, Rockville, MD 20855	Room 150 G -2773	ENERIU DHUB	FEB 117 199	6
Re: AADA 63-067 Minocycline Hy	vdrochloride Cans	ules USP, 100 mg	GENERIC DE	A.C.

Supplement: Removal of the Excess of Minocycline Hydrochloride USP, in the

Formulation and Increase of the Maximum Allowable Batch Size

Dear Dr. Ganley;

Reference is made to our currently approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 100 mg, which is manufactured at our facility in Lititz, Pennsylvania. At this time we would like to supplement our approved application to provide for a reformulation of the product to remove the excess of active drug substance, Minocycline Hydrochloride, USP. We would also like to incorporate increase in our maximum batch size for this product. Information to support these changes are provided in Attachments 1 through 7, as indicated. Our 50 mg capsule product is covered by a separate AADA (63-066), which is concurrently being supplemented for these changes.

Our currently approved formulation includes z excess of Minocycline Hydrochloride, USP. We desire to change our formulation for Minocycline Hydrochloride Capsules USP, for the 50 mg and 100 mg strength capsule products by removing this excess, and making an appropriate adjustment in the amount of o maintain the target capsule weight.

In accordance with this proposed formulation change, we have revised our composition page and our Master Formula to reflect the deletion of the excess of drug substance and our desired batch size of These revised AADA pages are contained in Attachments 1 and 2, respectively. Other changes are being proposed in the revised Master Formula. Many of these changes are editorial in nature; however, some enhancements have also been incorporated. For the convenience of the reviewer, we have summarized these changes immediately prior to the proposed master formula appearing in Attachment 2.

In support of this supplement, we have manufactured?

Hydrochloride Capsules USP, 100 mg, without the excess of Minocycline

Hydrochloride, USP. Our executed batch record (including complete packaging records) for lot 977N2L is included in Attachment 3. Warner Chilcott's Certificate of Analysis for this lot is provided in Attachment 4.

AADA 63-067
Dr. Charles Ganley
Minocycline Hydrochloride Capsules, USP

Provided in Attachment 5 is Warner Chilcott's Certificate of Analysis for a reference lot of Minocycline Hydrochloride Capsules USP, 100 mg (lot 637D2L). This lot is a routine production batch which was manufactured in accordance with our approved AADA; therefore, it contains ? excess of Minocycline Hydrochloride, USP. This lot served as the reference formulation for a single-dose bioequivalence study, which is discussed below.

Reference is made to the telephone conversation between Dr. S. Dighe, formerly of the Division of Bioequivalence, and Mr. V. Kumar, Warner Chilcott's former Director of Research and Development, on December 11, 1992 (as cited in a letter dated January 28, 1993). During this conversation, it was agreed that Warner Chilcott would conduct a bioequivalence study to support the removal of the excess from our current formula. We are submitting the final report of this bioequivalence study in Attachment 6. This single-dose, two-way crossover study compares the relative bioavailability of Warner Chilcott Minocycline HCl Capsules USP, 100 mg with and without a overage of Minocycline Hydrochloride, USP taken under fasting conditions (protocol #0801-5011).

Included in the final report for the above-mentioned bioequivalence study are the summary tables of the *in vivo* bioequivalence study, and comparative dissolution profiles for batches of both the 50 mg and 100 mg strength products, with and without the excess of Minocycline Hydrochloride, USP. Also included with the bioequivalence study is the analytical method used in this study for the determination of minocycline levels in human plasma and the validation data for the assay methodology.

In addition, we are submitting a computer diskette containing the raw data collected for this study. A hard copy of these data is provided in both review and archival copies of this application. A copy of the case report forms is also included in this submission as a separately bound volume.

Based on the results of this study and comparable formulations, our concurrent supplement for our 50 mg strength application (AADA 63-066) contains a request for a waiver of the requirement for an *in vivo* bioequivalence study, as permitted under 21 CFR 320.22 (d)(2). In support of this request we are including comparative dissolution data for 50 mg and 100 mg strength Warner Chilcott Minocycline Hydrochloride Capsules, USP with and without access of Minocycline Hydrochloride, USP.

Finally, we have included stability data for the reformulated product stored at 40°C/75% RH for 3 months and up to 24 months at 30°C packaged in our currently marketed package sizes (bottles of 50 and 1000 capsules) in Attachment 7. Based on the attached stability data, we are requesting an expiration dating period of 24 months for the reformulated product, which is the same as for our current formulation.

AADA 63-067
Dr. Charles Ganley
Minocycline Hydrochloride Capsules, USP

We trust that the enclosed information is satisfactory. In accordance with submission requirements, a field copy of this supplemental application is being concurrently submitted to our home district office in Newark, NJ. If you should require additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Corna Enders for Sean Brennan, Ph. D.

Senior Director Regulatory Affairs



Norma A. Enders, R.Ph. Senior Director. Regulatory Affairs

Mr. Douglas Sporn Director, Office of Generic Drugs Food and Drug Administration (CDER) Document Control Room Metro Park North II 7500 Standish Place, Room 150 Rockville, MD 20855-2773

January 8, 1997

SUPPL AMENDEMENT

Re: AADA #63-067

Minocycline Hydrochloride Capsules USP, 100 mg

Amendment to 11/27/96 Labeling Supplement Proposing the Addition of a Proprietary Name Submission of Final Printed Labeling

Dear Mr. Sporn;

Reference is made to our approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 100 mg, and to our supplemental application submitted on November 27, 1996, which provided labeling reflecting the addition of a proprietary name (Vectrin®) for our product.

Our pending labeling supplement had provided draft container labels and insert labeling for the Agency's review. However, we recognize that only final printed labeling will be approved by the Office of Generic Drugs. Since we wish to implement the Vectrin labeling by February 28, 1997, we are now amending the aforementioned supplement with final printed labeling.

Twelve final printed copies of our container labels for bottles of 20 capsules, 50 capsules, and 1000 capsules are provided in Attachments A, B, and C, respectively. Twelve final printed package inserts are provided in Attachment D. The twelve copies of each labeling piece are arranged as follows: six copies are provided in the archive copy and six copies are provided in the review copy of this submission. Please note that this labeling is identical in text to the draft labeling that was previously submitted. We refer you to our November 27, 1996 submission for a complete discussion regarding the differences between the Vectrin labeling and our currently approved labeling.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sincerely, RECEIVED

Transa Code

Norma Enders, R.Ph. 1997



Norma A. Enders, R.Ph. Senior Director, Regulatory Affairs

November 27, 1996

MARIE ST. 117 SLOID

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re:

AADA #63-067

Minocycline Hydrochloride Capsules USP, 100 mg Labeling Supplement: Addition of a Proprietary Name

Dear Mr. Sporn;

Reference is made to our approved antibiotic drug application for Minocycline Hydrochloride Capsules, USP, 100 mg. Reference is also made to the Office of Generic Drugs' Policy and Procedure Guide #20-90 (as amended on 6/7/95), entitled "Variations in Solid Oral Dosage Forms and Injectables that can be Included within a Single ANDA."

The above-referenced policy guide permits multiple colors of a single shape for a single strength of a solid oral dosage form to be included in the same abbreviated antibiotic drug application. It is our intention to add a second capsule color to this AADA. The second capsule color will be marketed with a proprietary name (Vectrin®) and our originally approved capsule color will continue to be marketed under the generic name. Please note that this new color was obtained via the deletion of specific dye components from our currently approved product. In accordance with 21 CFR 314.70(d)(4), this change does not require prior FDA approval and will be reported in the next annual report. This submission strategy was confirmed via telephone conversation between myself and Mr. P. Rickman of your staff on October 31, 1996.

The purpose of this supplemental application is to provide the Office of Generic Drugs with the opportunity to review and approve labeling that bears the Vectrin brand name. In an October 31, 1996 telephone conversation with Mr. John Grace, also of your staff, I was instructed that this supplement should be submitted for prior approval. While we believe that the regulations permit this change to be reported in the annual report (in accordance with 21 CFR 314.70(d)(2)), we wish to fully comply with Mr. Grace's recommendations. However, please note that we desire to implement this new labeling by February 28, 1997; therefore, we would appreciate any efforts that your staff can make in providing an expeditious review.

Please note that for completeness we have included a label for our bottles of 20 capsules package size. This size was originally approved as part of our initial AADA approval and was supported by completed stability studies. In pre-approval correspondence dated February 22, 1989, it was stated that the bottles of 20 capsules would be available for "Unit of Use" special contracts. We wish to have the option of using the unit of use bottles of 20 capsules for our Vectrin product. However, since this package size would not normally be commercially available, in accordance with 21 CFR 201.57(k)(2), we have not included the 20s package size on our proposed package insert.

Four copies of each of our draft labels and package insert labeling are provided in Attachments A through D. Please note that the attached labeling is identical to our currently approved labeling with the following modifications:

- 1) Addition of the Vectrin brand name and revised NDC numbers that are unique for the Vectrin product.
- 2) Revision of our company name and address to reflect the sale of Warner Chilcott by the Warner-Lambert Company and the subsequent relocation of our offices. (These actions were previously communicated to the AADA file in correspondence dated March 28, 1996 and November 21, 1996.)
- In addition to the above items, the package insert bears revisions in the "Description" section (removal of dye components from the inactive ingredients listing) and in the "How Supplied" section (revised product description, color, imprint, etc.).

Finally, we would like to point out that the Vectrin trade name was in use many years ago by Parke-Davis, Division of Warner-Lambert Company, when they distributed minocycline hydrochloride capsules under a licensing agreement with Lederle Laboratories. Warner Chilcott, Inc. has obtained the exclusive rights to the use of the Vectrin trademark. Since the Vectrin name was previously used for this same product, we were hoping that any review conducted by FDA's naming committee, if needed at all, could be handled in an expedited manner.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sincerely,

Norma A. Enders, R.Ph.

Sr. Director, Regulatory Affairs

WARNER CHILCOTT

LABORATORIES Division of Warner-Lambert Company

Sean Brennan, Ph.D. Senior Director Regulatory Affairs

Special Supplement -Changes Being Effected

Douglas Sporn

Director, Office of Generic Drugs

Food and Drug Administration (CDER)

Document Control Room

Metro Park North II

7500 Standish Place, Room 150

Rockville, MD 20855-2773

MAR 20 1996

REF. NO. 5L-009

NDA SUFFL FOR LAbeling Rev SL-009 AI

Re:

AADA #63-067

Minocycline Hydrochloride Capsules USP, 100 mg

Labeling Supplement

Girman ...

Dear Mr. Sporn:

This is in response to your letter dated February 5, 1996 in which you commented on the labeling for our abbreviated antibiotic drug applications for Minocycline Hydrochloride Capsules USP, 50 mg and 100 mg.

In your letter, you requested that we revise our package insert labeling for the subject product in accordance with the approved labeling of Minocin® (Lederle Laboratories Division, revised December 1993; approved August 8, 1995).

We have completed these revisions and are submitting twelve copies of our final printed insert labeling in Attachment A for your review.

We trust that the enclosed labeling is satisfactory. We are concurrently submitting a similar supplement to our 50 mg strength application (AADA #63-066). If you should require any additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Morma Enders jor Sean Brennan, Ph. D.

Senior Director

Regulatory Affairs

<u>APPLICATION NUMBER</u> 063066 /S011, 010, 009, 008, 007, 006

FINAL PRINTED LABELING

å ë date

₩ E

0687G000

N 0047-0687-11

Vectrin⊕ (minocycline hydrochloride capsules, USP)

50 mg (as the base)

Caution-Federal law prohibits dispensing without prescription

20 Capsules





N 0047-0687-11

Vectrin.

(minocycline hydrochloride

capsules, USP) 50 mg (as the base)

Caution—Federal law prohibits dispensing without prescription 20 Capsules WARNER CHILCOTT

MAY

Adult Dotage-200 mg initially, followed by 50 mg four times dolly. See plackage insert. Each capsule contains minocycline hydrochioide equivalent to 50 mg minocycline

Fach captule contains minocycline
hydrochlorde equivalent to 50 mg minocycline;
Adult Dosage-100 mg initiality, talicyled by 50 mg,
four times drifty See pockage insert

Dispense in a light, light-resistant container as TO defined in the USP Store at controlled room temperature 15°-30°C (59°-86°F), Protect from light.

Store of confolled room temperature 15: 30 c (59: 86 F). Protect from Hight.

Keep this and all drugs out of the reach of

Dispense in ty haht, light-resistant container as defined in the USP.

1007

Manufactured for, WARNER CHILCOTT, INC. 100 Enterprise Drive, Rockaway, 14, 078/6, 1)SA

Keep this and all drugs out of the reach of

Manufactured for: WARNER CHILCOTT, INC. 100 Enterprise Drive, Rackaway, NJ 07866, USA 3y: Wamer-Lambert Company Monts Plains, NJ 07950 USA - 6, 1996

Dispense in a light light-resistant container as defined in the USP.
Store of confrolled room temperature 15::30:c

Manufactured for: WARNER CHILCOTT, INC. 100 Enterprise Drive, Rockoway, Fill 07866, USA (eep this and all drugs out of the reach of



N 0047-0687-11

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0687G000

N 0047-0687-11

Vectrin. (minocycline hydrochloride capsules, USP)

50 mg

Caution-Federoi law prohibits dispensing without prescription.

20 Capsules



N 0047-0687-11

Vectrine (minocycline hydrochloride capsules, USP)

50 mg (as the base)

Caution-Federal law prohibits dispensing without prescription

20 Capsules



2 1997

Adult Dologe-200 mg initially, followed by 50 PQ four times dolby see package insert. Each capsule contains minacycline hydrochloride equivalent to 50 mg mhocyclinere

Each capsule contains minocycline hydrochorde equivolent to 50 mg minocycline TA Add Design 200 mg includiv tollowad by 50 mg four times daily. See pockage intent. Discense in a tight, light-resistant container as defined in the USP.

Store of controlled room temperature 15::30 C (59*-86*f), Protect from Eght. Keep this and all drugs cut of the reach of

Manufactured for WARNER CHILCOTT, INC. 100 Enterprise Drive, Rockoway, NJ 07866, USA By Wamer-Lambert Company Morts Plains, NJ 97950 1554 15005 0047-0687-11



0687G000

& 5



APR 24 1996

Minocycline HCI Capsules, USP

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4 S-(4a,4aa,5aa,12aa)]-4,7-Bis(dimethylamino)-1,4,4a,5aa,12aa)]-4,7-Bis(dimethylamino)-1,4,4a,5-(5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamide monohydrochloride, its structural formula is:

CzsHz7N3O7 • HCI

Each capsule, for oral administration, contains minocycline hydrochloride equivalent to 50 or 100 mg minocycline. In addition, each capsule contains the following inactive ingredients: megnesium stearate, NF and pregelatrized starch, NF (com). The capsule shell contains black iron oxide; FD&C blue #1; gelatin, NF; silicon dioxide, NF; sodium lauryl sultate, NF; tranium dioxide and yellow iron oxide. The 50-mg capsule shell also contains D&C red #28, D&C yellow #10, and FD&C red #240.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY
Following oral administration of minocycline hydrochloride capsules, absorption from the gastrointestinal tract is rapid. Following a single dose of minocycline hydrochloride administered to normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 4 hours. The serum half-life in normal volunteers ranged from approximately 11 hours to 22 hours.

hours.

When minocycline hydrochloride capsules were given concomitantly with a meal which included dairy products, the extent of absorption was not noticeably influenced. The peak plasma concentrations were signify decreased and delayed by one hour when administered with food, compared to dosing under fasting conditions.

in previous studies with minocycline hydrochlo-ride, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dys-function, and from 18 to 69 hours in 5 patients with renel dysfunction. The unnary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

Miscrobiology—The tetracyclines are primarily bacteriostatic and are thought to exert their animicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocy-cline, have eimiter arismicrobial spectra of activi-ty against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

White in vitro studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA: Bertonelle becilliformis Brucella species Campylobacter fetus Francisella tularensis semophilus ducreyi semophilus influenz

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recom-

Escherichia coli

bacteriostatic and are thought to exert their aritimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline, have similar aritimicrobial spectra of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

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GRAM-NEGATIVE BACTERIA:

GFAM-NEGATIVE BAK Bertonelle bacilitiormis Brucella species Campylobacter fetus Francisella tulareneis Haemophilus ducreyi Haemophilus influenzae Listeria monocytogenes Neisseria gonomoeae Vibrio chalerae Vibrio cholerae Yenninia passis

Personal pessas Because many strains of the tollowing groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recom-mended:

Acinetobacter species Bacteroides species Enteroides raerogenes Escherichia coli GRAM-POSITIVE BACTERIA

GRAM-POSITIVE BACTERIA:
Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and succeptibility testing are sepacially recommended. Up to 44 percent of Streptococcus progenes strains have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

Alpha hemolytic streptococci (viridans group) Streptococcus pneumoniae Streptococcus pyogenes

OTHER MICROORGANISMS

Actinomyces special Bacillus anthracis Balantidium coli Borrelia recum Chlamydia psittaci Chlamydia trachomatis Clostridium species Entamoeba species Fusobacterium fusiform Propionibactenum acnes Treponema pallidum Treponema pertenue

Ureaplasma urealyticum

Susceptibility Telegues—The use of antibiotic
Diffusion Techniques—The use of antibiotic
disk susceptibility test methods which measure
zone diameter gives an accurate estimation of
susceptibility of microorganisms to minocycline
HCI. One such standard procedure¹ has been
recommended for use with disks for testing
antimicrobials. Either the 30 mcg tetracycline-class disk or the 30 mcg minocycline
disk should be used for the determination of the
susceptibility of microorganisms to minocycline.

With this type of procedure a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptiblist" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg. urine) in which high antibiotic levels are attained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With either the tetracycline-class disk or the minocycline disk, zone sizes of 19 mm or greater indicate susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 18 mm indicate intermediate susceptibility.

Standardized procedures require the use of lab-

cate infermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mag tetracycline disk should give zone diameters between 19 and 29 mm for Staphylococcus aureus ATCC 25923 and between 18 and 25 mm for Escherichia coli ATCC 25922. The 30 mag minocycline disk should give zone diameters between 25 and 30 mm for S. aureus ATCC 25923 and between 19 and 25 mm for E. coli ATCC 25922.

ATCC 25922.

Distation Techniques—When using the NCCLS agar distan or broth distation (including incroditution) method² or equivalent, a bacterial isolate may be considered susceptible if the MIC (imminal inhibitory concentration) of minocycline is 4 mcg/mL or less. Organisms are considered resistant if the MIC is 16 mcg/mL or greater. Organisms with an MIC value of less than 16 mcg/mL ut greater than 4 mcg/mL are expected to be susceptible if a high diseage is used or if the infection is confined to issues and fluids (eg. urine) in which high antibiotic levels are attained.

As with standard diffusion methods, ditution pro-cedures require the use of laboratory control organisms. Standard letracycline or minocycline powder should give MIC values of 0.2 mog/mL to 1.0 mog/mL for S. eureus ATCC 25823, and 1.0 mcg/mL to 4.0 mcg/mL for E. coli ATCC 25922.

INDICATIONS AND USAGE

Minocycline hydrochloride capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group. O lever, notettainepox and tick fevers caused by Rickettsiee

if the intection is comment to inscend (eg. urine) in which high antibiotic levels are attained.

As with standard diffusion methods, disktion pro-cedures require the use of laboratory control organisms. Standard letracycline or minocycline powder should give MiC values of 0.25 mog/mL to 1.0 mog/mL for *S. sureus* ATCC 25923, and 1.0 mog/mL to 4.0 mog/mL for *E. coli* ATCC

INDICATIONS AND USAGE

Minocycline hydrochloride capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus tever and the typhus group, O tever, rickettsialpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by Mycoplasma pneumoniae.

Lymphogranuloma venereum caused by Chiarrydia trachometis.

Psittacosis (ornithosis) due to Chlamydia

Trachoma caused by Chlamydia trachomatis, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis caused by Chlamydia trachomatis.

Nongonococcal urethritis in adults caused by Ureaplasma urealyticum or Chlamydia trachomatis.

Relapsing fever due to Borrelia recurrentis

Chancroid caused by Haemophilus ducreyi.

Plague due to Yersinia pestis.

Tularemia due to Francisella tularensis.

Cholera caused by Vibrio cholerae.

Campylobacter fetus infections caused by Campylobacter fetus.

Brucellosis due to Brucella species (in conjunction with streptomycin).

Bartonellosis due to Bartonella bacilliformis.

Granuloma inguinale caused by Calymma-tobacterium granulomatis.

Minocycline is indicated for treatment of infec-tions caused by the following gram-negative microorganisms when bacteriologic testing indi-cates appropriate susceptibility to the drug:

Escherichia coli.

Shigella species. Acinetobacter species.

Respiratory tract infections caused by Haemophilus influenzae.

Respiratory tract and urinary tract infections caused by Klabsiella species.

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by Streptococcus pneumoniae.

Skin and skin structure infections caused by Staphylococcus aureus. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to Neisseria gonormoeae and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by Neisseria

Syphilis caused by Treponema pallidum.

Yaws caused by Treponema pertenue. Listeriosis due to Listeria monocytogenes.

Anthrex due to Becilius anthrecis.

Vincent's infection caused by Fuschacterium

Actinomycosis caused by Actinomyces

Infections caused by Clostridium speci

In acute intestinal amebiasis, minocycline may be a useful adjunct to amebicides.

In severe acne, minocycline may be useful adjunctive therapy.

adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptometric carmers of Neissens meninglikis to eleminate meningococci from the nasiopharyxx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcil carrier, desprostic taboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treat-ment of meningococcal infection.

mean or meanageucocas recuer.

Although no controlled clinical efficacy studies heve been conducted, limited clinical data show that oral minocycline hydrochloride has been caused successfully in the treatment of infections caused by Mycobacterium marinum.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetra-

WARNINGS

MINOCYCLINE HYDROCHLORIDE CAP-SULES, LIKE OTHER TETRACYCLINE-CLASS

Respiratory tract infections caused by Haemophikus influenzae.

Respiratory tract and urinary tract infections caused by Klebeiella species.

caused by Austroaceas special are indicat-ed for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate sus-ceptibility to the drug:

Upper respiratory tract infections caused by Streptococcus pneumoniae.

Skin and skin structure infections caused by Staphylococcus aureus. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to Neisserie gonombase and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an attemetive drug in the treatment of the following infections:

Infections in women caused by Neisseria genorrhosse.

Syphilis caused by Treponeme pallidum.

Yaws caused by Treponema persenue.

Listeriosis due to Listeria monocytogenes.

Anthrex due to Becilius anthracis.

Vincent's infection caused by Fusobacterium fusiforme.

Actinomycosis caused by Actinomyces

infections caused by Clostridium species.

In acute intestinal amebiasis, minocycline may be a useful adjunct to amebicides.

In severe acne, minocycline may be useful adjunctive therapy.

adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neissenie meninglitidis* to eliminate meningococci from the nesopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serolyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the nisk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treat-

Oral minocycline is not indicated for the treat-ment of meningococcal infection.

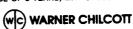
Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochoride has been used aucosstully in the treatment of infections caused by Mycobecterium marinum.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetra-

WARNINGS

WARNINGS
MINOCYCLINE HYDROCHLORIDE CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGNANCY WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LASS DURING TOOTH DEVELOPMENT (LASS DURING TOOTH AGE OF 8 YEARS) MAY CAUSE PERMA-



Minocycline HCI Capsules, USP

NENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

The adverse reaction is more comment during least-serm uses of the daug bet had belied observed todowing respected short-term courses. Enamel hypoplasia has also been reported. TETRACVCLINE DRUGS THE REFORE. SHOULD NOT BE USED TURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

CONTINUIDICATED.

All intracyclines form a stable calcium complex in any bone-forming liseue. A decrease in fibula growth rate has been observed in young animals (rates and rabbats) given or all tetracycline in disease of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was disconstrued.

Results of enimal studies indicate that tetracy-clines cross the placenta, are found in tetal te-sues, and can have tooc effects on the develop-ing fetus (often retested to retardation of elected development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy. The antianobritic scann of the tetracelines may

been noted in animals treated early in pregnancy. The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to excetenia, hyperhosphatemia, and acidosis. If renal impairment exists, even usual oral or per-enteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

may be advisible.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline.

reported rarely with minocycline.

Central nervous system side effects including lightheadedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

PRECAUTIONS

General

As with other antibiotic preparations, use of this
drug may result in overgrowth of nonsusceptible
organisms, including fungi. If superinfection
occurs, the antibiotic should be discontinued
and appropriate therapy instituted.

and appropriate therapy instituted.

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual crinical manifestations are headache and burned vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Incision and desirate or other survicel prope-

Incision and drainage or other surgical proce-dures should be performed in conjunction with antibiotic therapy when indicated.

Information for Patients
Information for Patients
Photosensitivity manifested by an exaggerated
surribum reaction has been observed in some
individuals taking tetracyclines. Patients apt to
be exposed to direct sunlight or ultraviolet light
should be advised that this reaction can occur
with tetracycline drugs, and treatment should be
discontinued at the first evidence of sion erytheman. This reaction has been reported rarely with
use of manocycline.

tee or remoposes.

Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy.

Concurrent use of tetracycline may render oral contraceptives less effective (see Drug Interactions).

Laborationy Tests In veneral desease when coexistent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

In long-term therapy, periodic liaboratory evalua-tions of organ systems, including hematopoistic, renal, and hepatic studies should be performed.

Drug interactions

Because tetracyclines have been shown to depress pleans prothrombin activity, patients who are on anticoaguiant therapy may require downward adjustment of their anticoaguiant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of peniciliin, it is advisable to avoid giving tetracycline-class drugs in conjunc-tion with peniciliin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and iron-containing preparations.

The concurrent use of tetracycline and methoxyllurane has been reported to result in tatal renel toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective.

Drug/Laboratory Test Interactions
False elevations of uniary catecholamine levels
more occur due to interference with the fluorescence test.

Carcinogeni of Fertility rsis, Mutagenesis, Impairment Dietary administration of minocycline in

Concurrent use of tetracyclines may render ora contraceptives less effective.

Drug/Leboratory Test Interactions
False elevations of urmary catecholamine levels
may occur due to interference with the fluores-

cence test.

Carcinogenesis, Mutagenesis, Impeliment of Fertility

Dietary administration of minocycline in long-term turnorigenicity studies in rats resulted in evidence of thyroid turnor production. Minocycline has also been found to produce thyroid hyperplasais in rats and dogs. In addition, there has been evidence of onogenic activity in rats in studies with a related artitiotic, conyterracycline (ie, adranal and pituitary turnors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in in vitro mammakan cell assays (ie, mouse lymphoma and Chenese hemster lung cells) have been reported for related artibiotics (tetracycline). Segment I (fertility and general reproduction) studies have provided evidence that minocycline impeirs fertility in male rats.

Terstogenic Effects: Pregnancy: Pregnancy Casegory D (see WARNINGS).

Labor and Delivery
The effect of tetracyclines on labor and delivery

Nursing Mothers
Tetracyclines are excreted in human milk.
Because of the potential for serious adverse

reactions in nursing infants from the tetracy-clines, a decision should be made whether to discontinue nursing or discontinue the drug, tak-ing into account the importance of the drug to the mother (see WARNINGS).

Pediatric Use: see WARNINGS.

ADVERSE REACTIONS

Due to oral minocycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhee, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and increases in lever enzymes. Rarely, hepatitis and iver failure have been reported. Rare instances of esophagitis and esophagial ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

Skin: Maculopapular and enythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Fixed drug enuptions, including bai-aritis, have been rarely reported. Erythema mul-tiforms and rarely Stevens-Johnson syndrome have been reported. Photosensitivity is dis-cussed above (see WARNINGS). Pigmentation of the skin and mucous membrane

Renal toxicity: Elevations in BUN have been reported and are apparently dose related (see WARNINGS).

Hypersensitivity reactions: Urticaria, angioneu-rotic edema, polyarthralgia, enaphytaus, ana-phylactoid purpura, pencarditis, exacerbation of systemic lupus erythematosus and rarely pul-monary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome has also been reported.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and ecsinophilia have been reported. Central nervous system: Bulging fontanels in infants and benign intracranial hypertension (pseudotumor cerebri) in adults (see PRECAUTIONS—General) have been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid glands. Very rare cases of abnormal thy-roid function have been reported.

Tooth discoloration in pediatric patients less than 8 years of age (see WARNINGS) and also, rarely, in adults have been reported. Decreased hearing has been rarely reported in patients on minocycline hydrochloride.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive

DOSAGE AND ADMINISTRATION

THE USIAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF MINOCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Minocycline hydrochloride capsules may be taken with or without food.

ADULTS: The usual dosage of minocycline hydrochloride capsules is 200 mg initially followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

by one 30 mg capacie foot arries casey.

FOR PEDIATRIC POPULATION ABOVE 8

YEARS OF AGE: The usual decage of minocycline hydrochloride capaules is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum or four days, with post-therapy cultures within 2 to 3 days. cultures within 2 to 3 days.

In the treatment of uncomplicated genococcal

hydrochlonde capsules is 200 mg initially towed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially tollowed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of minocycline hydrochloride capsules is 4 mg/kg initially tollowed by 2 mg/kg every 12 hours.

tollowed by 2 mg/kg every 12 inclusion.

Uncomplicated gonococcal infections other than urethritis and ancrectal infections in men: 200 mg initially, tollowed by 100 mg every 12 hours or a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men. 100 mg every 12 hours for five days is recommended.

usys is recommended.

For the treatment of syphilis, the usual dosage of minocycline hydrochloride capsules should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for five days.

Mycobacterium marinum intections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by Chlampidia trachomatis or Uneaplasma urealyticum: 100 mg orally, every 12 hours for at least seven days.

Income for at least seven cays.

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal imitation and ulceration.

In patients with renal impairment (see WARN-INGS) the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses.

HOW SUPPLIED

Minocycline hydrochloride capsules USP, equivalent to 50 mg or 100 mg minocycline, are sup-

50 mg olive and brown, size #3, capsules imprinted WC 615:
Bottles of 100
Bottles of 1000
N 0047-0615-32

100 mg white and olive, size #2, capsules imprinted WC 616:
Bottles of 50 N 0047-0616-19
Bottles of 1000 N 0047-0616-32

Storage Conditions: Store at controlled room temperature 15°-30° C (59°-86° F). Protect from light.

Caution—Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY AND

TOXICOLOGY

TOXICOLOGY
Minocycline HCI has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minipigs, dogs, and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in gotter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs. REFERENCES

REFERENCES

- National Committee for Clinical Laboratory Standards, Approved Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests, 3rd Edition, Vol. 4(16): M2-A3, Villanova, PA. December 1984.
- rA. Lecember 199.

 2. National Committee for Clinical Laboratory Standards, Approved Standard: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 2nd Edition, Vol. 5(22): M7-A, Villanova, PA. December 1985.

0615G025

Revised February 1996

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WARNER CHILCOTT LABS Div of Warner-Lambert Co Morris Plains, NJ 07950 USA Vectrin_® (minocycline hydrochloride capsules, USP)

100 mg

20 Capsules WARNER CHILCOTT

Manufactured for: WABNER CHILCOTT, INC. 100 Enterprise Drive, Rockaway, NJ 07866, USA © 1994

APN

each capsule contains minocycline hydrochionae equivalent to 100 mg minocycline.

Adult Dosage 200 mg initialy, followed by 100 mg twice daily, See pockage fixed.

1 4 1997

Manufactured for: WARNER CHITCOTT, INC. 100 Enterprise Drive, Rockaway, NJ 07866, USA

0688G020

06886000

₽ N 0047-0688-19

Vectrine (minocycline hydrochloride capsules, USP)

100 mg

-federal law prohibits ng without prescription.



효호

0688G030

100 mg



N 0047-0688-32

Vectring (minocycline hydrochloride capsules, USP)

(as the base)

Caution—Federal law prohibits dispensing without prescription.

1000 Capsules

Manufactured for: WARNER CHILCOTT, INC. 6 100 Enterprise Drive Rockaway, NJ 07866, USA

Keep this and all drugs out of the reach of children

Vectrin® 0687G010





(minocycline hydrochloride capsules, USP)

DESCRIPTION

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4 5-44α, 4aα, 5aα, 12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride, its structural tomula is:

CzzHzzNzOz • HCI

Each Vectrin capeule, for oral admir Each Vectrin capsule, for oral administration, contains minocycline hydrochloride equivalent to 50 or 100 mg minocycline. In addison, each capsule contains the following inactive impediants: magnesium stearate. NF and pregetatriaxed starch, NF (com). The capsule shell contains gelatin, NF; sincon disoxide, NF; sodium lauryl sulfate, NF; and titanium dioxide. The 50-mg capsule shell also contains D&C yellow \$10, and FD&C red \$40. The 100-mg capsule shell also contains FD&C blue \$1.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY
Following oral administration of minocycline hydrochloride capsules, absorption from the gastronisistinal fract is rapid. Following a single dose of minocycline hydrochloride administered to normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 4 hours. The serum half-life in normal volunteers ranged from approximately 11 hours to 22 hours.

When minocycline hydrochloride capsules were given concomitantly with a meal which included dairy products, the earter of ebsorption was not noticeably influenced. The peak plasms concen-trations were signify decreased and delayed by one hour when administered with food, com-pared to desing under fasting conditions.

pared to downg under tessing conditions. In previous studies with minocycline hydrochlo-nde, the minocycline serum helf-life ranged from 11 to 16 hours in 7 patents with hepatic dys-function, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

White in vitro studies have demonstrated the succeptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA: Bertonella bacilliformis Brucella species Campylobacter fetus Francisella tutarensis Heemophilus ducreyi a gonor

use many strains of the following groups of i-negative microorganisms have been in to be resistant to tetracyclines, culture usosptibility tests are especially recom-

While in vitro studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than tinose included in the NEDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:

Bartonella bacilliromis
Brucella species
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzi Listeria monocytoge Neissena gonomhoe Vibrio cholerae Yersinia pestis

retrains possible because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclimiss. culture and susceptibility tests are especially recommended:

Acinetobacter species Bacteroides species Enterobacter serogenes da species Shioella species

Shigelia species
GRAM-POSITIVE BACTERIA:
Because many strains of the following groups of
gram-positive microorganisms have been
shown to be resistant to tetracyclines, culture
and susceptibility testing are especially recommended. Up to 44 percent of Streptococcus
spaggeres strains have been lound to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcus
assessmites the organism has been demonstrated to be susceptible.

Alpha hemolytic streptococci (viridans group) Streptococcus pneumoniae Streptococcus pyogenes

OTHER MICHOORGANISMS: OTHER MICHOUNGS
Actinomyces species
Bacillus arthracis
Balantidium coli
Borreta recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species Chlamydia tracromais Clostridium species Entamoeba species Fusobacterium fusiforme Propionibacterium acnes Treponema paliidum Treponema pertenue Ureaplasma urradyticum

Treponents pertenue Unaplasma unalyticum
Susceptibility Teets
Diffusion Techniques—The use of antibiotic disk susceptibility teets methods which measure zone diameter gives an accurate estimation of susceptibility of microorganisms to minocycline HCI. One such standard procedure! has been recommended for use with disks for teeting antimicrobials. Either the 30 mcg terracycline-class disk or the 30 mcg minocycline disk should be used for the 40 mcg minocycline with this type of procedure a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if a high diosage is used or if the infection is confined to tissues and fluids (eg. unme) in which high aribitotic levels are attained. A report of "resistant" indicates that the infection organism is not likely to respond to therapy. With either the tetracycline-class disk or the minocycline disk, zone sizes of 19 mm or greater indicate susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 18 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disk-procedures require the use of laboratory control organisms. The 30 mcg tetracycline.

cate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mog tetracycline disk should give zone diameters between 19 and 28 mm for Staphylococcus aureus ATCC 25923 and between 18 and 25 mm for Escherichia coli ATCC 25922. The 30 mcg minocycline disk should give zone diameters between 25 and 30 mm for S. aureus ATCC 25923 and between 19 and 25 mm for E. coli ATCC 25929.

ATCC 25822.

Distation Techniques—When using the NCCLS sign distation or broth distation (including microdistation) method² or equivalent, a bacterial isolate may be considered susceptible if the MC (minimal inhibitory concentration) of minocycline is 4 mog/ml, or less. Organisms are considered resistant if the MC is 16 mog/ml, or greater. Organisms with an MIC value of less than 16 mog/ml, but greater than 4 mog/ml, are expected to be susceptible if a high dosage is used or if the infection is confirmed to bissues and fluids (eg. urine) in which high antibiotic levels are statemed.

As with standard diffusion methods, diution pro-cedures require the use of laboratory control organisms. Standard istracycline or minocycline powder should give MIC values of 0.25 mog/mL to 1.0 mog/mL tor S. aureus ATCC 25623, and 1.0 mog/mL to 4.0 mog/mL for E. coli ATCC 25922.

INDICATIONS AND USAGE

Vectrin capsules are indicated in the treatment of the following infections due to susceptible strains of the designated

Rocky Mountain spotted fever, typhus fever and the typhus group. O fever, rickettsialpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by Lymphogranuloma venereum caused by Chlemydie trachometis.

Psittacosis (ornithosis) due to Chlamydia

INDICATIONS AND USAGE

Vectrin capsules are indicated in the treatment of the following infections due to susceptible strains of the designated

Rocky Mountain spotted fever, typhus fever and the typhus group, O tever, rickettsielpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by

Lymphogranuloma venereum caused by Chlarnydia trachomatis.

Psittacosis (ornithosis) due to Chlamydia

Trachome caused by Chlamydia trachomatis, aithough the infectious agent is not always eliminated, as judged by immunofluores-

inclusion conjunctivitis caused by Chlamydia trachomatis.

Nongonococcal urethritis in adults caused by Ureaplasma urealyticum or Chlamydia tra-Ureaplasi chomats

Relapsing fever due to Borrelia recurrentis.

Chancroid caused by Haemophilus ducreyi.

Plague due to Yersinia pestis.

Tularemia due to Francisella tulare

Cholera caused by Vibrio cholerae.

Campylobacter fetus infections caused by mpylobacter fetus.

Brucellosis due to Brucella species (in conjunction with streptomycin).

Bartonellosis due to Bartonella bacilliformis.

Granuloma inguinale caused by Calymmatobacterium granulomatis.

Minocycline is indicated for treatment of intec-tions caused by the following gram-negative microorganisms when bacteriologic testing indi-cates appropriate susceptibility to the drug:

Escherichia coli. Enterobacter aerogenes.

Shigelie species.

Acinetobacter species.

Respiratory tract infections caused by Haemophilus influenzae.

Respiratory tract and unnary tract infections caused by Klebsiella species.

Vectrin capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by

Skin and skin structure infections caused by Staphylococcus aureus. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in, men due to Neisseria gonorhosea and for the treatment of other gonococcal infections when penicilin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the tollowing infections: Infections in women caused by Neisseria

aonomh

Syphilis caused by Treponems pelidum. Yaws caused by Treponema pertenue.

Listeriosis due to Listeria monocytogenes.

Anthrax due to Bacillus anthracis.

Vincent's infection caused by Fusobactenum

Actinomycosis caused by Actinomyces

Infections caused by Closindium spaces.

In acute intestinal amebiasis, minocycline may be a useful adjunct to amebicides.

In severe acre, Vectrin may be useful adjunc-tive therapy.

tive therapy.

Oral manocycline is indicated in the treatment of asymptomatic carmers of Nassenie meninglicids to eliminate meninglococc from the reacopharynix. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meninglococcal carmer, diagnostic laboratory procedures, including serolyting and susceptivity testing, should be performed to establish the carmer state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningolococcal meningles is high.

Oral minocycline is not indicated for the treat-

Oral minocycline is not indicated for the treet ment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been caused successfully in the treatment of infections caused by Mycobecterium mannium.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARHINGS

WARNINGS
VECTRIN CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE
FETAL HARM WHEN ADMINISTERED TO A
PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF
THE PATHENT BECOMES PREGNANT WHILE
TAKING THESE DRUGS.THE PATIENT
SHOULD BE APPRISED OF THE POTENTIAL
HAZARD TO THE FETUS THE USE OF

piratory tract and unnary tract infected by Klebeistle spaces.

Vectrin capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate succeptibility to the drug:

Upper respiratory tract infections caused by Streptococcus pneumoniae.

Skin and skin structure infections caused by Staphylococcus aureus. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to Naisseria gonomboaee and for the treatment of other gonococcal infections when penicillin is contrandicated.

When penicillin is contraindicated, minocycline is an atternative drug in the treatment of the following infections:

Infections in women caused by Neissena gonorhoose.

Syphilis caused by Traponems pallidum

Yaws caused by Treponema pertenue.

Listeriosis due to Listena monocytogenes

Anthrax due to Bacillus anthracis.

Vincent's infection caused by Fusibactenum

Actinomycosis caused by Actinomyces

Infections caused by Clostridium species

In acute intestinal amebiasis, minocycline may be a useful adjunct to amebicides.

In severe acne, Vectrin may be useful adjunctive therapy.

tive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of Neeseen meningledis to eliminate meningococci from the nesopharysis. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, disgnostic laboratory procedures, including serolyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningits is high.

Oral minocycline is not indicated for the treat-ment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochlonde has been used successfully in the treatment of infections caused by *Mycobactenum mannum*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

WARNINGS

VECTRIN CAPSULES. LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS. CAN CAUSE
FETAL HARM WHEN ADMINISTERED TO A
PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY. OR IF
THE PATIENT BECOMES PREGNANT WHILE
TAKING THESE DRUGS. THE PATIENT
SHOULD BE APPRISED OF THE POTENTIAL
HAZARD TO THE FETUS. THE USE OF
DRUGS OF THE TETRACYCLINE CLASS
DURING TOOTH DEVELOPMENT (LAST
HALF OF PREGNANCY. INFANCY. AND
CHILDHOOD TO THE RGE OF 8 YEARS) MAY
CAUSE PERMANENT DISCOLORATION OF
THE TEETH (YELLOW-GRAY-BROWN).



v ectrin-

This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS. THEREFORE. SHOULD NOT BE USED DURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED. CONTRAINDICATED.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in young animals (rats and rabbits) given oral tetracycline in dease of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was

Results of animal studies indicate that tetracy-cines cross the placenta, are found in test te-sues, and can have took celects on the develop-ing tetra (often related to retardation of sixtettal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

been noted in animals treated early in pregnancy. The antenabolic action of the tetracyclines may cause an increase in BUN. White this is not a problem in those with normal renal function, in patients with significantly impaired function, in patients with significantly impaired function, in patients with a sprincantly impaired function, in the problems of the distracycline may lead to accommand ones may lead to exceeding oral or perentenal diseas may lead to exceeding systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline.

Central nervous system side effects including lightheadedness, dizziness, or vertigo have been reported with minocycline therapy. been reported with minocycline inelapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocy-cline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

PRECAUTIONS

General

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsucceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

and appropriate interapy instituted. Pseudolumor cerebri (berign infracranial hyper-tension) in adults has been associated with the use of tetracyclines. The usual clinical manifes-tations are headsche and blurred vision. Bulging lontanels have been associated with the use of tetracyclines in infrants. While both of free con-ditions and related symptoms usually resolve after discontinuation of the tetracycline, the pos-sibility for permanent sequelee exists.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

antibiotic therapy when indicated.

Information for Patients
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patents apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of sitin eytherma. This reaction has been reported rarely with use of minocycline.

Patents who emprisons central persons see-

Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. Concurrent use of tetracycline may render oral contraceptives less effective (see Drug Interactions).

Laboratory Tests In veneral desise when consistent syphile is suspected, a dert-field examination should be done before treatment is seared and the blood serology repeated monthly for at least four

in long-term therapy, penodic leboratory evalua-tions of organ systems, including hematopoistic, renal, and hepatic studies should be performed.

Drug Interactions
Because tetracyclines have been shown to deprese pleams profrombin activity, patents who are on anticogulant therapy may require downward adjustment of their anticoagulant

Since bacteriostatic drugs may interfere with the bacterioddal action of perioditin, it is advisable to avoid giving tetracycline-class drugs in conjunction with perioditin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or mag-nesium, and iron-containing preparations.

The concurrent use of tetracycline and methoxyllurane has been reported to result in tatal renal toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective.

Drug/Laboratory Test Interactions False elevations of unnary catecholamine levels may occur due to interference with the fluores-bence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Drug/Laboratory Test interactions Feliae elevations of urinary catecholamine levels may occur due to interference with the fluores-cence test.

Carcinogenesis, Mutagenesis, Impeliment of Fertility
Dietary administration of minocycline in tong-term tumorgenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs, in addition, where has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxyletracycline (ie, adrenal and pituitary tumors). Litewise, atthough mutagenicity studies of minocycline have not been conducted, positive results in in vitro mammakan cell assays (ie, mouse) impronoma and Chinisee hamster lung cells) have been reported for resisted antibiotics (totracycline hydrochlorids and oxyletracycline). Segment I (tersitry and general reproduction) studies have provided evidence that minocycline impairs tertility in mile rats.

Terassgenic Effects: Pregnancy: Pregnancy

Teratagenic Effects: Pregnancy: Pregnancy Category D (see WARNINGS).

Labor and Delivery
The effect of tetracyclines on labor and delivery is unknown.

is unknown.

Nursing Mothers
Tetracyclines are excreted in human milk.
Because of the potential for senous solverse
reactions in nursing intents from the tetracydires, a decision should be made whether to
discontinue nursing or discontinue the drug, taking into account the importance of the drug to
the mother (see WARNINGS).

Pediatric Use: see WARNINGS.

ADVERSE REACTIONS

Due to oral minocycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

patients receiving tetracyclines.
Gastroinestinal: Anorexie, neusea, vomiting, derma, gloselis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monital overgrowth) in the anogenital region, and increases in tiver enzymes. Rarely, hepsitis and liver failure have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTMATION).
Skin: Maculopspular and erythematious rashes.
Extiniative dermatitis has been reported but is uncommon. Fixed drug eruptions, including balanitis, have been rarely reported. Enythema multiforme and rarely Stevens-Johnson syndrome have been reported. Photocenstrivity is discussed above (see WAPNINGS). Prigmentation of the skin and mucous membranes has been

Renal toxicity: Elevations in BUN have been reported and are apparently dose related (see reported and WARNINGS).

Hypersenuitivity reactions: Urticana, angione Hypersenutivity reactions: Unicaria, anythin ex-rotic edema, polyarimajae, anaphylaxis, ana-phylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and rarely pul-monary infiltrates with ecenophilia have been reported. A transient lupus-like syndrome has also been reported.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Central nervous system: Bulging tontanets in infants and benign intracranial hypertension (pseudotumor cerebri) in adults (see PRECAUTIONS—General) have been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid glands. Very rare cases of abnormal thyroid function have been reported.

ruot un un reive useri reportero.

Tooth discoloration in pediatric patients less than 8 years of age (see WARNINGS) and also, rarely, in adults have been reported. Decreased hearing has been rarely reported in patients on minocycline hydrochloride.

OVERDOBAGE

In case of overdosage, decontinue medication, treat symptomatically and institute supportive

DOBAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF MINOCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Minocycline hydrochloride capsules may be taken with or without food.

ADULTS: The usual dosage of Vectrin (minocycline hydrochlonde capsules) is 200 mg initially followed, by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of Vectrin (minocycline hydrochloride capsules) is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

initially tollowed gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 der 3.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for five

FÜR PÉDIATRIG PÜPÜLATION ABOYE C YEARS OF AGE: The usual dosage of Vactori (minocycline hydrochorde capacies) is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections of men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for five days is recommended.

tays a recommendation. For the treatment of syphilis, the usual desage of Vectrin (minocycline hydrochloride capsules) should be admiristered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

in the treatment of meningococcal camer state, the recommended dosage is 100 mg every 12 hours for five days.

Mycobacterium mannum infections: Although optimal doses have not been detablished. 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by Chlamydia trachomatis or Uneaplasma unealyscum: 100 mg orally, every 12 hours for at least seven days.

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of esophagael imitation and ulceration.

in patients with renal impairment (see WARN-INGS) the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses

HOW SUPPLIED

Vectrin (minocycline hydrochloride capsules USP), equivalent to 50 mg or 100 mg minocy-cline, are supplied as:

50 mg orange opaque, size #3, capsules imprinted Vectrin 50 mg: Bottles of 100 N 0047-0687-24 Bottles of 1000 N 0047-0687-32

100 mg blue opaque, size #2, capsules imprinted Vectrin 100 mg.
Bottles of 50 N 0047-0688-19
Bottles of 1000 N 0047-0688-32

Storage Conditions: Store at controlled room temperature 15"-30" C (59"-86" F). Protect from light.

Caution—Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Minocycline HCI has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minipigs, dogs, and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplease in rats and dogs.

REFERENCES

- National Committee for Clinical Laboratory Standards, Approved Standard: Performance Standards for Animicrobial Disk Susceptibility Tests, 3rd Edition, Vol. 4(16): M2-A3, Villanova, PA. December 1984.
- National Committee for Clinical Laboratory Standards, Approved Standard: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 2nd Edition, Vol. 5(22): M7-A, Villanova, PA. December 1985.

0687G010

Issued November 1996

Manufactured for: WARNER CHILCOTT, INC. 100 Enterprise Drive Rockaway, NJ 07866 USA

By: Warner-Lambert Company Morris Plains, NJ 07950 USA



APR 24 1996

Minocycline HCI Capsules, USP

DESCRIPTION

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4 S-4a, 4ac, 5ac, 12ac)]-4,7-Bis(dimethylamino)-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochlonde, its structural formula is:

CzyHzyNyOy • HCi

Each capsule, for oral administration, contains minocycline hydrochlonde equivalent to 50 or 100 mg minocycline. In addition, each capsule contains the following inactive ingredients: megnesium stearate, NF and pregelatinized starch, NF (com). The capsule shell contains black iron oxide; FD&C blue #1; gelatin, NF; shoon dioxide, NF; sodium lauryl sultate, NF; ttanium dioxide and yellow iron oxide. The 50-mg capsule shell also contains D&C red #28, D&C yellow #10, and FD&C red #28.

CLINICAL PHARMACOLOGY

Following oral administration of minocycline hydrochloride capaules, absorption from the gastrointestinal tract is rapid. Following a single dose of minocycline hydrochloride administered to normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 4 hours. The serum half-life in normal voluntaers

When minocycline hydrochloride capsules were given concomitantly with a meal which included dairy products, the extent of absorption was not noticeably influenced. The peak plasma concen-trations were slightly decreased and delayed by one hour when administered with food, com-pared to doeing under fasting conditions.

pared to downg under tasting conditions. In previous studies with minocycline hydrochlo-nide, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepsic dys-function, and from 18 to 89 hours in 5 patents with renal dysfunction. The uninary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

that of other tetracyclines. Microbiology—The tetracyclines are primarily bacteriostatic and are thought to easer their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline, have similar aritmicrobial spectra of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

white in vitro studies have demonstrated the succeptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA: Bartonelle beciliformis Brucelle species

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recom-mended:

GRAM-POSITIVE BACTERIA: Because many strains of the following groups of gram-positive microorganisms have been

viono choierae Yerainia pastis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recom-

Bacteroides apecies Enterobacter aeroge Encherichie coli Klebsiella species Shigella species

GRAM-POSITIVE BACTERIA

GRAM-POSITIVE BACTERIABecause many strains of the following groups of gram-positive microorganisms have been shown to be resustant to tetracyclines, culture and susceptibility testing are especially recom-mended. Up to 44 percent of Streptococcus progenes strains have been found to be resis-tant to tetracycline drugs. Therefore, tetracy-clines should not be used for streptococcal dis-cesse unless the organism has been demonstrat-ed to be susceptible.

Alpha hemolytic streptococci (viridens group) Streptococcus pneumonine Streptococcus pyogenes

OTHER MICROORGANISMS: Actinomyces specie Bacillus antirracis Balantidium coli Borrelia recumentis Chlamycia pattaci Chamydia trachomatis Clostridium species
Clostridium species
Entamosba species
Fusobacterium fusiforme
Propionibacterium acnes Treponema pallidum Treponema pertenue Ureaplasma urealyticui

Urapiesma urealyticum
Susceptibility Tests
Diffusion Techniques—The use of antibiotic disk susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of microorganisms to minocycline HCI. One such standard procedure! has been recommended for use with disks for testing antimicrobials. Either the 30 mcg tetracycline-class disk or the 30 mcg minocycline disk should be used for the determination of the susceptibility of microorganisms to minocycline.

With this type of procedure a report of "auscept-ble" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to trasues and fluids (eg, urine) in which high antibiotic levels are attained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With either the tetracycline-class disk or the minocycline disk, zone sizes of 19 mm or greater indicate susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 18 mm indicate intermediate susceptibility.

Standardized procedures require the use of lab-

case intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mog tetracycline disk should give zone diameters between 19 and 28 mm for Staphylococcus sureus ATCC 25923 and between 18 and 25 mm for Escherichia coli ATCC 25922. The 30 mog minocycline disk should give zone diameters between 25 and 30 mm for 5. aureus ATCC 25923 and between 19 and 25 mm for E. coli ATCC 25927.

ATCC 25922.

Dilution Techniques—When using the NCCLS agar disulton or broth dilution (including microdistron) method 2 or equivalent, a bacterial isolate may be considered susceptible if the MIC (innimal inhibitory concentration) of minocycline is 4 mcg/mL or less. Organisms are considered resistant if the MIC is 16 mcg/mL or greater. Organisms with an MIC value of less than 16 mcg/mL but greater than 4 mcg/mL are expected to be susceptible if a high dosage is used or if the infection is confined to bases and fluids (eg. urine) in which high antibiotic levids are attained.

As with standard diffusion methods, dilution pro-cedures require the use of laboratory control organisms. Standard istracycline or minocycline powder should give MIC values of 0.25 mog/mil. to 1.0 mog/mil. to 4.0 mog/mil. for E. coli ATCC 25922.

INDICATIONS AND USAGE

Minocycline hydrochlonde capaules are indicated in the treatment of the following infections due to succeptible strains of the designated microorgeniems:

Rocky Mountain spotted fever, typhus fever and the typhus group. O fever, richetteistpox and tick levers caused by Rickettman.

Respiratory tract infections caused by

Lymphogranuloma venereum caused by Chlamydia trachomatis.

Psittacosis (ornithosis) due to Chlamydia

Trachoma caused by Chlemydie #achomess, although the infectious agent is not always eliminated, as judged by immunofluores-

Inclusion conjunctivitis caused by Chlemy trachomatis.

Nongonococcal urethritis in adults caused by Ureaplasma ureallyticum or Chlamydia tra

Releasing lever due to Borrelia recur Chancroid caused by Hasmophilus ducreyi. Plague due to Yersinia pestis

Minocycline hydrochloride capsules are indicated in the treatment of the following intections due to susceptible strains of the designated microorpanisms:

Rocky Mountain epotted lever, typhus lever and the typhus group, Q lever, ricketsistpox and tick levers caused by Rickettaise.

Respiratory tract infections caused by

Lymphogranuloma venereum caused by Chlemydia trachomatis.

Psittacosis (ornithosis) due to Chlamydia

Trachoma caused by Chlamydia s'achomais. although the infectious agent is not always eliminated, as judged by immunofluores-

inclusion conjunctivities caused by Chil

Nongonococcel urethrine in adults caused by Ureacisems ureal/sicum or Chlemydia fra-

ing lever due to Barrelie recur

Chancroid caused by Heamophilus ducreyi.

Please due to Yersinia pastis

Tularemia due to Francisella Mili

Cholera caused by Vibrio cholerae.

Campylobacter fetus infections caused by Campylobacter fetus.

Brucellosis due to Brucelle species (in conunction with streptomycin).

Bertonellosis due to Bertonelle becilik

Granuloma ingunale caused by Calymma-tobacterium granulomats.

Minocycline is indicated for treatment of infec-tions caused by the following gram-negative microorganisms when bacteriologic testing indi-cates appropriate succeptibility to the drug:

Enterobacter aerogenes.

Shipale species.

Respiratory tract infections caused by Heamophilus influenzae.

Respiratory tract and urinary tract infections caused by Klabaielle species.

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by Streptococcus pneumoniae.

Sign and ston structure infections caused by Stephylococcus aureus. (Note: Minocycline is not the drug of choice in the treatment of any type of stephylococcal infection.)

Uncomplicated urethritis in men due to Neisseria gonombase and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicitin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by Neisseria

Syphilis caused by Traponema pallidum.

Yaws caused by Traponema pertenue.

Listeriosis due to Listeria monocytogenes.

Anthrax due to Becillus anthracis.

Vincent's infection caused by Fusobacterium

Actinomycosis caused by Actinomyces

Infections caused by Clostridium species.

In acuse intestinal amebiasis, minocycline may be a useful adjunct to amebicides.

in severe acne, minocycline may be useful adjunctive therapy.

adjunctive therapy.

Onel memocycline is indicated in the treatment of asymptometric carriers of Nesserie meningibids to alternate meningibids to alternate meningibids to alternate meningibids to alternate meningibids. In order to preserve the usertuness of menocycline in the treatment of asymptometric meningibids, including serolyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the first of meningibids meninges is high.

Onel minocycline is not indicated for the treat-

Oral minocycline is not indicated for the tre-ment of maningococcal infection.

ment or mentinguous interest.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used aucosefully in the treatment of relactions caused by Mycobacterium marinum.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetra-

WARNINGS

WARNINGS
MINOCYCLINE HYDROCHLORIDE CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGRANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE

Respiratory tract infections caused by Heamophius infunzae.

Respiratory tract and urinary tract infections caused by Klebsielle species.

Minocycline hydrochloride capeules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate autoaptibility to the drug:

Upper respiratory tract infections caused by Streptococcus pneumonise.

Skin and skin structure infections caused by Staphylococcus aureus. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to Neissene ganombose and for the treatment of other ganococcal infections when perscillin is contraindicated.

When perioditin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by Newsense ganarrhoses.

Syphilis caused by Treponeme pallidum.

Yaws caused by Treponema persenue.

Listeriosis due to Listeria monocytogenes.

Anthrax due to Becilius antivacis.

Vincent's infection caused by Fueobacterium huitonne

Actinomycosis caused by Actinomyces

infections caused by Clostridium species.

In acute intestinal amediasis, minocycline may be a uteful adjunct to amedicides.

In severe acne, minocycline may be useful adjunctive therapy.

adjunctive therapy.

Oral minocycline is indicated in the treatment of saymptomatic camers of Neisseria meningides to eliminate meningococci from the neacoharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcii carrier, diagnostic laboratory procedures, including serolyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcial meningies is high.

Oral minocycline is not indicated for the treat-

Oral minocycline is not indicated for the treat-ment of maningococcal infection.

nems or mesimpotoccas snections.

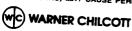
Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used aucoessiuly in the treatment of infections caused by Myoobsclerium marinum.

CONTRAINDICATIONS

This drup is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines

WARNINGS

WARNINGS
MINOCYCLINE HYDROCHLORIDE CAPSULES, LIKE OTHER TETRACYCLINE-CLASS
ANTIBIOTICS, CAN CAUSE FETAL HARM
WHEN ADMINISTERED TO A PREGNANT
WOMAN, IF ANY TETRACYCLINE IS USED
DURING PREGNANCY, OR IF THE PATIENT
BECOMES PREGNANT WHILE TAKING
THESE DRUGS, THE PATIENT SHOULD BE
APPRISED OF THE POTENTIAL HAZARD TO
THE FETUS. THE USE OF DRUGS OF THE
TETRACYCLINE CLASS DURING TOOTH
DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE
AGE OF 8 YEARS) MAY CAUSE PERMA-



Minocycline HCI Capsules, USP

NENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

This adverse reaction is more common during This solvene reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplesia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

All latracyclines form a stable calcium complex in any bone-forming issue. A decrease in floute growth rate has been observed in young animals (rats and rabbits) given oral letracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was decontinued.

Results of animal studies indicate that tetracy-clines cross the piscents, are found in fetal te-sues, and can have toxic effects on the develop-ing fetus (often related to retardation of sixlettal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

been noted in animals treated early in pregnancy. The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to accessive, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or per-enteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicasted, and if therapy is prolonged, serum level determinations of the drug may be advessible. may be advisable.

Photoeensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline.

repurse rarely win minocycane.

Central nervous system side effects including lighthreadedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

PRECAUTIONS

General
As with other antibiotic preparations, use of this
drug may result in overgrowth of nonsusceptible
organisms, including fungi. If superinfection
occurs, the antibiotic should be discontinued
and appropriate therapy instituted.

erto appropriate therapy instituted.

Passudotumor carebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Budging fontanels have been associated with the use of tetracyclines in intants. While both of these conditions and related symptoms usually recoive after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

antibiotic therapy when indicated. Information for Patients Photosensitivity mainlested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with setracycline drugs, and treatment should be discontinued at the first evidence of skin erythe-ma. This reaction has been reproted ramly with

Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous mechinery while on minocycline therapy.

Concurrent use of telescycline may render oral contraceptives less effective (see Drug Interactions).

In veneral desses when consistent syphile is suspected, a def-held examination should be done before treatment is started and the blood serology repeated monthly for at least four

In long-term therapy, periodic leboratory eval-tions of organ systems, including hometopole renal, and hepatic studies should be performe

Drug interactions
Because tetracyclines have been shown to depress plasma prothrombon activity, pasents who are on anticoagulant therapy may require downward adjustment of their anticoagulant

Since bacteriostatic drugs may interfere with the bacteriodal action of peniotiin, it is advisable to avoid giving tetracycline-class drugs in conjunction with peniotiin.

Absorption of tetracyclines is impaired by antecide containing summum, calcium or magnesium, and iron-containing preparations.

The concurrent use of tetracycline and methoxyllurane has been reported to result in latel renel toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective.

DrugfLaboratory Test Interactions
False elevations of urinary catecholemens levels
may occur due to interference with the fluorescence test.

reis, Mutagenesis, Impair

Drug/Laboratory Test Interactions False elevations of unnery catecholamine levi may occur due to interference with the fluore

Carcinogeneals, Mistaganeals, Imparviolet of Fertility
Dietary administration of minocycline in long-term tumorigenicity studies in rate resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasals in rate and dogs, in addition, there has been evidence of oncogenic activity in rate in studies with a related artistotic, conylettic (ie, adrenal and pituitary tumors). Litewise, atthough mutagenicity studies of minocycline have not been conducted, positive results in in vitro mammakan cell easays (e. mouse lymphoma and Chinese hamster lung cells) have been reported to related artistosics (tetracycline hydrochloride and crystatracycline). Segment I (fertility and general reproduction) studies have provided evidence that minocycline impairs fertility in male rate.

Terratogenic Effects: Pregnancy: Pregnancy

Teratogenic Effects: Pregnancy: Pregnancy Category D (see WARNINGS).

Labor and Delivery
The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers Tetracyclines are excreted in human milk. Because of the potential for serious adverse

reactions in nursing intents from the tetracy-clines, a decision should be made whether to decontinue nursing or decontinue the drug, tak-ing into account the importance of the drug to the mother (see WARNINGS).

Pediatric Use: see WARNINGS.

ADVERSE REACTIONS

Due to oral minocycline's virtually complete absorption, side effects to the lower bowel, particularly diarrises, have been intraquent. The following adverse reactions have been observed in patients receiving tetracyclines.

patients recoving serecyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, ensercicitis, inflammatory teaions (with monital overgrowth) in the anogenital region, and increases in liver enzymas. Rarely, hapsitis and increases in liver enzymas. Rarely, hapsitis and esophageal utcerstons have been reported in patients taking the tetracycline-class artibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see ication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION).
Sian: Maculopapular and enythematous rashes. Exiolative dermatitis has been reported but is uncommon. Found drug eruptions, including balantis, have been rarely reported. Enythema multiforme and rarely Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above (see WARNINGS). Pigmentation of the skin and mucous membranes has been reported. reported.

Renal toxicity: Elevations in BUN have been reported and are apparently dose related (see WARNINGS).

Hypersensitivity reactions: Unicaria, angioneu-rotic edema, polyarihralgia, anaphysixis, ana-physicioti purpura, penicardise, essentisten of systemic lupus erythematosus and ramity pul-monary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome has

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eceinophilia have been reported.

Central nervous system: Bulging fontanels in infants and benign intracranial hypertension (pseudolumor osrebi) in adults (see PRECAUTIONS—General) have been reported.

TONS—cantrag invertible reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic decoloration of the thysoid glands. Very rare cases of abnormal thyroid function have been reported.

Tooth discoloration in pediatric patients less than 8 years of age (see WARNINGS) and also, rarely, in adults have been reported. Decreased hearing has been restly reported in patients on minocycline hydrochloride.

OVERDOBAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF MINOCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Minocycline hydrochloride capsules may be taken with or without food.

ADULTS: The usual dosage of minocycline hydrochloride capsules is 200 mg initially followed by 100 mg every 12 hours. Alternatively, if more trequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of minocycline hydrochloride capsules is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated genococal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

towed by 100 mg every 12 hours. Attermativery, it more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosege of minocycline hydrochronice capsules is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated genococal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four deys, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for five days is recommended.

toys is recommended. For the treatment of syphilits, the usual desage of minocycline hydrochloride capsules should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal center state, the recommended dosage is 100 mg every 12 hours for five days.

Mycobacterium marinum infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by Chlamydia trachomatis or Unapleame ureelyscum: 100 mg crally, every 12 hours for at least seven days.

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of ecophageal irritation and ulceration.

in the state of the series of

HOW SUPPLIED

Minocycline hydrochloride capeules USP, equivalent to 50 mg or 100 mg minocycline, are sup-

50 mg olive and brown, size #3, capsules imprinted WC 615:
Bottles of 100 N 0047-0615-24
Bottles of 1000 N 0047-0615-32

100 mg white and olive, size #2, capsules imprinted WC 616:
Bottles of 50 N 0047-0616-19
Bottles of 1000 N 0047-0616-32

Storage Conditions: Store at controlled room temperature 15°-30° C (59°-86° F). Protect from light.

Caution—Federal law prohibits depending with out prescription.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Minocycline HCI has been observed to cause a Minocycline HCI has been observed to cause a dark discoloration of the thyroid in superimental animals (rate, minipigs, dogs, and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in golder accompa-nied by elevated radioactive indine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplassis in rate and dogs. REFERENCES

- National Committee for Clinical Laboratory Standards, Approved Standard: Performance Standards for Animicrobial Disk Susceptibility Tests, 3rd Edition, Vol. 4(16): M2-A3, Villanovs, PA. December 1984.
- PA. December 1984.

 2. National Committee for Clinical Laboratory Standards, Approved Standard: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria Hat Grow Aprobiasity, 2nd Edition, Vol. 5(22): M7-A, Villanova, PA. December 1985.

0615G025

Revised February 1996

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WARNER CHILCOTT LABS Div of Warner-Lambert Co Morris Plains, NJ 07950 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

<u>APPLICATION NUMBER</u> 063066 /S011, 010, 009, 008, 007, 006

CHEMISTRY REVIEW(S)

<u>AADA</u> 63-066/S-006, 007 63-067/S-006, 007

NAME AND ADDRESS OF APPLICANT:

Warner Chilcott, Inc. 182 Tabor Road Morris Plains, NJ 07950

PURPOSE OF AMENDMENT/SUPPLEMENT

S-006: To provide for elimination of the overage of active drug substance in both

potencies of this drug product.

prevent accidental transfer of

S-008: Stability data to support an expiration date of 24 months for the revise formulas.

DATE(S) OF SUBMISSION(S)
Submission not dated - received 3/1/96.

PHARMACOLOGICAL CATEGORY TRADE NAME NONPROPRIETARY NAME

PHARMACOLOGICAL CATEGORY
Antibacterial

TRADE NAME
N/A

Minocycline Hydrochloride

DOSAGE FORM POTENCY RX OR OTC

Capsules 50 mg R
100 mg

SAMPLES RELATED IND/NDA/DMF STERILIZATION N/A N/A

LABELING N/A

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS N/A

PACKAGING

N/A

STABILITY

N/A

REMARKS AND CONCLUSION

The firm obtained approval for these applications with a access of drug substance in the formulation. They now propose to eliminate this overage (S-006). The approved formulation for 100 mg capsule (as revised in Y-003, submitted 12/3/93) and the proposed revision are presented below for comparison. The approved and proposed revisions for the 50 mg capsules are proportional.

100 mg CAPSULE:

INGREDIENTS

UNIT FORMULA

BATCH FORMULA

PER CAPSULE:

APPROVED PROPOSED APPROVED PROPOSED

Minocycline HCl Pregel. Starch Magnesium Stearate

Target Fill Weight

270.0 mg

270.0 mg

Notes: 1.

- Equivalent to 100 mg minocycline as base per capsule pli cess at 100% potency.
- 2. Equivalent to 100 mg minocycline as base per capsule at 100% potency.
- 3. The amount of sadjusted for the amount of minocycline hydrochloride added, the total weight required to equal mg per capsule.

The firm discussed this proposed change with the Division of Bioequivalence in December of 1992. At that time the firm concluded from this conversation (with Dr. Dighe) that a Bio study was needed to support the removal of the excess from the formula. However, it appears from an examination of the letter in the file that, during the conversation, Dr. Dighe consulted the Orange Book and decided that since this drug product is rated AB, no study was needed. In any event the firm did do a study on the 100 mg strength and have submitted the results. Dr.

Moheb Makary discussed this with me and, after consulting Mr. Harrison, I told Dr. Makary that we normally would not expect a biostudy to delete an overage. He indicated that was fortunate since the study suffered from a flawed design. He stated that he would waive the study rather than review it.

The firm also introduces a prevent accidenta¹ will be increased at 24 months.

step for the minocycline and intended to (S-007). The batch size The expiration dating would remain the same

Information submitted in support of these submissions includes:

- 1. Copies of the revised Master Formulas.
- 2. Batch records for exhibit batches of 00 mg capsules and 0 mg capsules.
- 3. COA's for reference lots of each strength and COA's for each exhibit batch.
- 4. Comparative dissolution studies of batches made with and without the excess.
- 5. 3 months accelerated stability data and 24 months data at 30°C for each strength.
- 6. Development report demonstrating that the addition of the coarse screening step does not effect the particle size of the drug product (Attachment 2).

These supplement are approvable.

<u>RECALLS</u>

Reviewer

Date Completed

N/A

R.C.Adams

6/5/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 063066 /S011, 010, 009, 008, 007, 006

BIOEQUIVALENCE REVIEW(S)

Minocycline HCl 50 mg and 100 mg Capsules AADA #63-066 (50 mg) AADA #63-067 (100 mg) Reviewer: Moheb H. Makary

63067SDW.396

Warner Chilcott Laboratories Morris Plains, NJ Submission Date: March 1, 1996

Review of a Bioequivalence Study, Dissolution Data and Waiver Request

I. Objective:

The firm submitted these two supplements to provide for a reformulation for its Minocycline HCl, 100 mg and 50 mg Capsules to remove the excess of active drug substance, Minocycline HCl, USP, and making an appropriate adjustment in the amount of to maintain the target capsule weight.

The firm also plans to incorporate a increase in the maximum batch size for the 100~mg strength. The firm's 50~mgcapsule product is covered by a separate AADA (63-066), which is concurrently being supplemented for these changes.

To support the removal of the from the current formula the firm has submitted a single-dose, two-way crossover bioequivalence study comparing the relative bioavailabilty of Warner Chilcott Minocycline HCl Capsules, USP, 100 mg with and without a overage of Minocycline HCl, USP, taken under fasting conditions. The firm also submitted comparative dissolution profiles for batches of both the 50 mg and 100 mg strengthproducts, with and without the excess of Minocycline HCl, USP. The firm requested a waiver of in vivo bioequivalence study requirements for its Minocycline HCL, 50 mg Capsule.

II. Background:

Warner Chilcott Laboratories had previously conducted an acceptable in vivo bioequivalence study (a single-dose study under fasting conditions) on its Minocycline HCl Capsule, 100 mg which includes a excess of Minocycline HCl, USP. Waiver was granted for the 50 mg strength which also includes a Minocycline HCl, USP. The firm has held an approved AADA #63-067 for Minocycline HCl, 100 mg Capsule and AADA #63-066 for Minocycline HCl, 50 mg Capsule since July 31, 1990.

III. <u>In Vivo Results</u>:

Fourteen (14) healthy male subjects (12 plus two alternates) participated and completed the study.

The plasma minocycline concentrations (ng/mL) following administration of test lot A (without overage) and reference lot B (with 5% overage) are shown in Table I. The 90% confidence

intervals (log-transformed) for ${\rm AUC}_{\rm (0-TLOQ)},~{\rm AUC}_{\rm inf}$ and ${\rm C}_{\rm max}$ are shown in Table II.

The data demonstrate that there are no statistically significant differences for minocycline between the test and reference lots for $AUC_{(0-TLOQ)}$, AUC_{inf} and $C_{max.}$ The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

IV. <u>Dissolution Data</u>:

The firm has submitted comparative dissolution data on its previously approved minocycline HCl 100 mg and 50 mg Capsules (with a excess of Minocycline HCl) and reformulated products (without a excess of Minocycline HCl and with adjustment in the amount of using the following dissolution conditions:

Test product: Warner Chilcott's reformulated Minocycline

HCl Capsules

100 mg, lot #977N2L 50 mg, lot #976N2L

Reference product Warner Chilcott's previously approved

Minocycline HCl Capsules

100 mg, lot #637D2L 50 mg, lot #13013L

Method: USP 23, apparatus II (paddle) at 50 rpm.

Medium: 900 mL of water

Number of Tablets: 12

Specifications: NLT in 45 minutes.

Dissolution testing results are shown in Table III.

V. Formulations:

Warner Chilcott's reformulated and previously approved Minocycline HCl Capsules, 100 mg and 50 mg are shown below:

Component	Mino Reformula 50 mg	cycline HC ted 100 mg		y Approved 100 mg
Minocycline HCl USP Pregelatinized Starch, NF Magnesium Stearate	54.0ª	108.0 ^b	56.7	113.4
Target Fill Weight	220.0	270.0	220.0	270.0

^{*} Equivalent to 50 mg of minocycline as base per capsule at 100% potency (theoretical equivalent of minocycline HCl is 92.6%). This weight will be further adjusted upon the results of the potency test.

- b The amount of is adjusted for the amount of minocycline HCl added. The total weight for minocycline HCl and should equal 217.8 mg per capsule.
- c Equivalent to 100 mg of minocycline as base per capsule at 100% potency (theoretical equivalent of minocycline HCl is 92.6%). This weight will be further adjusted upon the results of the potency test.
- d The amount of is adjusted for the amount of minocycline HCl added. The total weight for minocycline HCl and should equal 267.3 mg per capsule.

VI. <u>Comments</u>:

- 1. The bioequivalence study conducted by Warner Chilcott Laboratories on it reformulated Minocycline HCl 100 mg Capsule, lot #977N2L comparing it to the previously approved formulation containing excess Minocycline HCl (AADA #63-067, Minocycline HCl 100 mg Capsule, approval dated July 31, 1990) is acceptable. However, the firm should have conducted the bioequivalence study on its the reformulated product comparing it to the reference listed product Minocin 100 mg Capsules manufactured By Lederle Laboratories instead of its previously approved product.
- 2. Dissolution results for the reformulated products Minocycline HCl 100 mg and 50 mg Capsules are acceptable as summarized in Table III.
- 3. Since the amounts 54.0 mg and 108.0 mg of Minocycline HCl for the 50 mg and 100 mg strengths are equivalent to 50 mg and 100 mg, respectively, of minocycline as base per capsule at 100% potency (theoretical equivalent of minocycline HCl is 92.6%). And based on USP 23 specifications, the Minocycline HCl Capsules should contain the equivalent of not less than 90.0% and not more than 115.0% of the labeled amount of minocycline. The request to remove the excess of active drug substance, Minocycline HCl, USP, from the firm's Minocycline HCl, 50 mg and 100 mg Capsules may be granted.
- 4. Adjustments the amount of for Minocycline HCl Capsules, 100 mg and 50 mg are covered under SUPAC-IR, November 1995, Level 1 Changes (i.e., acceptable dissolution testing).

VII. Recommendations:

1. The dissolution testing conducted by Warner Chilcott Laboratories on its reformulated Minocycline HCl 100 mg and 50 mg Capsules, lot #977N2L and 976N2L, respectively, is acceptable. Waivers of in vivo bioequivalence study requirements for the test products are granted. From the bioequivalence point of view, the Division of Bioequivalence deems the reformulated Minocycline HCl 100 mg and 50 mg Capsules to be bioequivalent to the firm's

previously approved Minocycline HCl 100 mg and 50 mg Capsules and for which the firm currently holds an approved AADAs.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of drug in the dosage form are dissolved in 45 minutes

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D. Division of Bioequivalence Review Branch III

	TIALLED RMHATRE TIALLED RMHATRE	Date: 6/25/96
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Concur	Keith Chan, Ph.D. Director Division of Bioequivalenc	Date: 6/27/56

MM/6-25-96/wp 63067SDW.396 cc: AADA # 63-067 and #63-066 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Makary), Drug File, Division File.

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Minocycline HCl 100 mg and 50 mg Capsules

Dose Strength: 50 mg and 100 AADA No.:63-066 and 63-067

Firm: Warner Chilcott Laboratories Submission Date: March 1, 1996

File Name: 63067SDW.396

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM:50

No. Units Tested: 12 Capsules

Medium: 900 mL of water

Specifications:NLT in 45 minutes

Reference Drug: Warner's previously approved Minocycline HCl

100 mg and 50 mg Capsules

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes)	Test Product Lot # 977N2L, without 5% excess of Minocycline HCl Strength(mg) 100		Reference Product Lot # 637D2L, with 5% excess of Minocycline HCl Strength(mg) 100			
	Mean %	Range	%CV	Mean %	Range	%CV
15	96		2.7	98		1.4
30	101		1.2	98		1.4
45	100		1.3	99		1.4
60	102		1.2	99		1.3
Sampling Times Minutes)	Lot # 976N2L, without 5%		Reference Product Lot # 13013L, with 5% excess of Minocycline HCl Strength(mg) 50			
	Mean %	Range	%CV	Mean %	Range	%CV
15	93		2.9	100		1.6
30	97		2.0	102		1.6
			1.6	103		2.0
45	98	<u> </u>	1	1 2 0 0	L	<u> </u>
60	98		1.4	104		1.6

Table I

TABLE

A comparison of arithmetic mean (%RSD) plasma minocycline concentrations (ng/mL) following administration of test lot A (without overage) and test lot B (with 5% overage)

£	T			
Time (hours)	Lot A	Lot B	Ratio A/B	Statistical Significance
0	0	0		NSD
0.5	294(82)	332(105)	0.89	NSD
1.0	1095(45)	1123(41)	0.98	NSD
2.0	1288(18)	1332(16)	0.97	NSD
3.0	1240(14)	1228(15)	1.01	NSD
4.0	1163(15)	1187(17)	0.98	NSD
6.0	934(15)	974(17)	0.96	NSD
8.0	754(12)	780(18)	0.97	NSD
12	564(16)	560(18)	1.01	NSD
16	442(15)	449 (20)	0.98	NSD
24	302 (24)	294(28)	1.03	NSD
36	176(25)	180(34)	0.98	NSD
48	92(31)	91(47)	1.01	NSD
60	59(36)	60(59)	0.98	NSD
72	35(65)	26(116)	1.35	NSD

Lot A:

Test lot A (without overage) administered under fasting

conditions.

Lot B:

Test lot B (with

overage) administered under fasting

conditions.

Ratio

Lot A/Lot B:

Ratio of arithmetic means of Lot A/Lot B.

Statistical

Significance:

Statistical significance of the ratio comparison.

NSD:

No Significant Difference (p > 0.05).

Table I

TABLE 7 Mean minocycline parameters and a statistical comparison of the test lot A (without overage) to the test lot B (with overage)

	AUC _(0-TLQC)	AUC _(0-INF)	C _{MAX}	Т	т	
-	AUC _(0-TLQC) AUC _(0-INP) C _{MAX} T _{MAX} T _{1/2} Arithmetic Means (%RSD)					
Lot A: No overage	21392(16)	22370(17)	1412 (17)	2.07 (48)	15.2 (14)	
Lot B: With overage	21530(21)	22481(22)	1417 (13)	1.79 (50)	14.4 (19)	
4	Lea	ast Squares Me	eans 👯			
Lot A: No overage	21392	22370	1412	2.07	15.2	
Lot B: With overage	21530	22481	1417	1.79	14.4	
Ratio Lot A / Lot B	99.4%	99.5%	99.6%	116%	106%	
Shortest 90% CI	95-104%	95-104%	93-106%	86-145%	97-114%	
Geometric Means						
Lot A: No overage	21135	22090	1394		·	
Lot B: With overage	21154	22046	1406			
Ratio Lot A / Lot B	99.9%	100%	99.2%			
Shortest 90% CI	96-104%	96-104%	93-106%	·		
Statistical Significance for Non-Transformed Data						
Lot A vs Lot B	NSD	NSD	NSD	NSD	NSD	
Statistical Significance for Log Transformed Data						
Lot A vs Lot B	NSD	NSD	NSD			

MINOCYCLINE HCI 100 MG CAPSULE MEAN DATA (N=14 SUBJECTS)

